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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 February 1999 (04.02.99)	
International application No. PCT/IE98/00036	Applicant's or agent's file reference FB3782/MOC
International filing date (day/month/year) 14 May 1998 (14.05.98)	Priority date (day/month/year) 14 May 1997 (14.05.97)
Applicant PASSMORE, Clare et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
14 December 1998 (14.12.98)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Yolaine CUSSAC Telephone No.: (41-22) 338.83.38
---	--

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IE 98/00036

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/107 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991 see page 5; example 1 ---	1, 2, 9, 14-18 3-8, 10-13
X	WO 97 04728 A (ZHANG ET AL.) 13 February 1997 see page 18, line 14 - line 31 ---	1, 2, 9, 14-18
X	A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US) see page 365 --- -/-	1, 2, 9, 14-18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

28 September 1998

Date of mailing of the international search report

08/10/1998

Name and mailing address of the ISA

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

Int. tional Application No

PCT/IE 98/00036

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992 see page 7, line 8 - line 12 see page 20 - page 21; example 3 -----</p>	1,2,9,14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IE 98/00036

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9104733 A	18-04-1991	AU 6504190 A CA 2067131 A EP 0493496 A GB 2239600 A JP 5502440 T	28-04-1991 27-03-1991 08-07-1992 10-07-1991 28-04-1993
WO 9704728 A	13-02-1997	US 5658583 A AU 6638696 A EP 0857047 A	19-08-1997 26-02-1997 12-08-1998
EP 485207 A	13-05-1992	US 5206021 A AT 153499 T AU 659616 B AU 8702291 A CA 2055133 A CN 1061132 A CS 9103343 A DE 69126275 D DE 69126275 T DK 485207 T ES 2104674 T FI 915243 A GR 3024545 T JP 4288002 A OA 9748 A PT 99441 A TR 25517 A	27-04-1993 15-06-1997 25-05-1995 14-05-1992 08-05-1992 20-05-1992 13-05-1992 03-07-1997 15-01-1998 22-12-1997 16-10-1997 08-05-1992 31-12-1997 13-10-1992 30-11-1993 30-09-1992 01-05-1993

CLAIMS

1. A topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each
5 discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous - phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C.
- 10 2. A topical composition according to Claim 1, in which the first pharmacologically active agent has a melting point between 35 and 75°C, preferably 40-50°C, and the second pharmacologically active agent has a melting point between -40 and 150°C, preferably between -5 and 90°C.
- 15 3. A topical composition according to Claim 1 or 2, in which the topical composition additionally includes, in the eutectic mixture, a third pharmaceutically acceptable component.
4. A topical composition according to Claim 3, in which the
20 third pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.
5. A topical composition according to Claim 3 or 4, in which the third component is a third pharmacologically active agent.
- 25 6. A topical composition according to any one of Claims 3-5, in which the topical composition additionally includes, in the eutectic mixture, a fourth pharmaceutically acceptable component.

7. A topical composition according to Claim 6, in which the fourth pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.

8. A topical composition according to Claim 6 or 7, in
5 which the fourth component comprises a fourth pharmacologically active agent.

9. A topical composition according to any one of the preceding claims, in which said compositions contain no co-solvent or additional oil phase, so that the eutectic mixture
10 substantially, preferably ~~essentially~~, comprises the or each discontinuous phase of the emulsion.

10. A topical composition according to any one of the preceding claims, in which the first pharmacologically active agent is selected from triclosan, chlorocresol, chlorbutanol, methyl nicotinate, triprolidine, promethazine, trimeprazine,
15 sulfiram, oxybutynin, capsaicin, testosterone enanthate or choline salicylate.

11. A topical composition according to any one of the preceding claims, in which the second pharmacologically
20 active agent is selected from triclosan; chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid
25 derivatives such as etodolac; and arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; anthelmintics such as
30 tetramisole; antihistaminics such as triprolidine and promethazine and antihypertensives such as propranolol.

12. A topical composition according to Claim 5 or 8, in which the third and fourth pharmacologically active agents are each selected from triclosan; chlorocresol; capsaicin, trimeprazine, choline salicylate, methyl nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; antihypertensives such as propranolol; antihistaminics such as triprolidine and promethazine; and anthelmintics such as tetramisole.
13. A topical composition according to Claim 3 or 4, in which the third pharmaceutically acceptable component is lauric acid, stearyl alcohol, menthol, thymol, cinnamic acid or an ester thereof.
14. A topical composition according to any one of the preceding claims, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier containing substantially, preferably essentially, water as the continuous phase.
15. A topical composition according to any one of the preceding claims, in which the pharmaceutically acceptable carrier contains at least one gelling or suspension agent.
16. A topical composition according to Claim 15, in which the gelling or suspension agent is selected from carbomers, modified cellulose derivatives, naturally-occurring, synthetic or semi-synthetic gums such as xanthan gum, acacia and tragacanth, modified starches, co-polymers such as those

formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylate derivatives or a mixture thereof.

17. A topical composition according to any one of the
5 preceding claims, in which the pharmaceutically acceptable carrier includes at least one surfactant compatible with any pharmacologically active agents or pharmaceutically acceptable components present.

18. A topical composition according to any one of the
10 preceding claims, in which the topical composition is in the form of a gel, lotion, suspension, cream, aerosol spray, transdermal patch, medicated dressing or soft gelatin capsule.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference FB3782/MOC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IE 98/ 00036	International filing date (day/month/year) 14/05/1998	(Earliest) Priority Date (day/month/year) 14/05/1997
Applicant GALEN (CHEMICALS) LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☐ the text is approved as submitted by the applicant
 - ☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. _____ ☐ as suggested by the applicant. ☐ None of the figures.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IE 98/00036

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The invention concerns a topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°. The topical composition may additionally comprise, in the eutectic mixture, a third or fourth pharmaceutically acceptable component.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/IE 98/00036

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K9/107 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991 see page 5; example 1 ---	1, 2, 9, 14-18 3-8, 10-13
X	WO 97 04728 A (ZHANG ET AL.) 13 February 1997 see page 18, line 14 - line 31 ---	1, 2, 9, 14-18
X	A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US) see page 365 ---	1, 2, 9, 14-18
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

28 September 1998

Date of mailing of the international search report

08/10/1998

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IE 98/00036

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992 see page 7, line 8 - line 12 see page 20 - page 21; example 3 -----</p>	1, 2, 9, 14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IE 98/00036

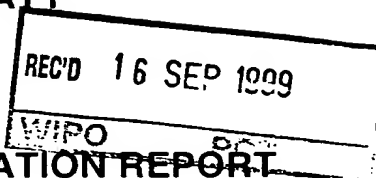
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9104733 A	18-04-1991	AU 6504190 A CA 2067131 A EP 0493496 A GB 2239600 A JP 5502440 T	28-04-1991 27-03-1991 08-07-1992 10-07-1991 28-04-1993
WO 9704728 A	13-02-1997	US 5658583 A AU 6638696 A EP 0857047 A	19-08-1997 26-02-1997 12-08-1998
EP 485207 A	13-05-1992	US 5206021 A AT 153499 T AU 659616 B AU 8702291 A CA 2055133 A CN 1061132 A CS 9103343 A DE 69126275 D DE 69126275 T DK 485207 T ES 2104674 T FI 915243 A GR 3024545 T JP 4288002 A OA 9748 A PT 99441 A TR 25517 A	27-04-1993 15-06-1997 25-05-1995 14-05-1992 08-05-1992 20-05-1992 13-05-1992 03-07-1997 15-01-1998 22-12-1997 16-10-1997 08-05-1992 31-12-1997 13-10-1992 30-11-1993 30-09-1992 01-05-1993

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference FB3782/MOC		FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IE98/00036	International filing date (day/month/year) 14/05/1998	Priority date (day/month/year) 14/05/1997	
International Patent Classification (IPC) or national classification and IPC A61K9/107			
Applicant GALEN (CHEMICALS) LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14/12/1998	Date of completion of this report 14.05.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Simon, F Telephone No. +49 89 2399 2083 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IE98/00036

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20 as originally filed

Claims, No.:

1-24 as received on 20/08/1999 with letter of 19/08/1999

Drawings, sheets:

1-9 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 21,23.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IE98/00036

- ☒ the said international application, or the said claims Nos. 21,23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20,22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20,22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-20,22
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

I

The amendments filed with the letter dated 19.08.1999 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following: present claim 24 deals with eutectic mixtures of specific compounds. Even though said specific compounds are mentioned in examples A-I and examples 3 and 6 in the description as filed, said compounds are only disclosed in relation to a specific ratio for which the eutectic mixture is liquid at 20°C (see eg example B and fig. 2), in a specific composition (see example 3, "emulsified gel preparation suitable for treating allergic and inflammatory pruritic skin compositions") and only for exactly two compounds and not for at least two compounds. Present claim 24 does not refer to each of these features and its subject-matter is therefore broader than that disclosed in the application as filed.

III

The subject-matter of claims 21 and 23 is directed to a method for treatment of the human body by therapy (Art. 34(4)(a)(i) and Rule 67.1(iv) PCT).

V

1 Reference is made to the following documents:

D3: WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991

D4: WO 97 04728 A (ZHANG ET AL.) 13 February 1997

D5: A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US)

D6: EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992

2 Novelty (Art. 33(2) PCT)

The subject-matter of present claims 1-20 and 22 fulfills the requirements of Art. 33(2) PCT.

2.1 Document D3 (see D3, page 3, lines 3-10 and eg. example 3 on page 6)

discloses eg a composition containing a eutectic solution of 4 g ibuprofen and 4 g menthol, also mixed with benzyl alcohol, carbomer and water. However, none of the compositions of D3 contains an emulsifying agent. Therefore, the subject-matter of present independent claim 1 and present independent claim 22 is new over D3.

2.2 Document D4 discloses a formulation, which is a gelled oil-in-water emulsion with an oil phase being a eutectic mixture of local anaesthetics. In a particular embodiment (see D4, example 1, page 18), the composition comprises an aqueous continuous phase with a polymeric emulsifier and an oil phase consisting of a eutectic mixture of lipocaine and tetracaine stated as being liquid at room temperature. However, present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. Thus, present independent claims 1 and 22 are new over D4.

2.3 Document D5 discloses a topical anaesthetic formulation based on a 1:1 eutectic mixture, having an eutectic temperature of 18°C, of lidocaine and prilocaine, emulsified in water. Present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. For this reason, present independent claims 1 and 22 are new over D5.

2.4 Document D6 discloses a stabilized pesticidal emulsion of the oil-in-water type (see D6, page 4, lines 39-45) comprising (see D6, pages 20-21, example 3):

- an oil phase consisting of two pesticides: 191 g/l (2,4-dichlorophenoxy)acetic acid isooctyl ester (2,4-D IOE) and 208 g/l (2,4-dichlorophenoxy)propionic acid isooctyl ester (2,4-DP IOE),
- a water phase containing surfactants and thickeners.

Even though said pesticides are ingredients which are pharmacologically active and are liquid at room temperature (see D6, page 19, lines 33- 37 and page 7, lines 8-12), present independent claim 1 and present independent claim 22 refer to topical compositions for mutual enhancement of transdermal permeation of pharmacologically active ingredients. It is clear that compositions containing pesticides, ie substances which are virtually toxic to humans, are not topical compositions suitable for transdermal permeation in the meaning of the present application.

3 Inventive step (Art. 33(3) PCT)

Document D4 is devoted to an apparatus, a product formulation and a method for improved dermal permeation of pharmaceuticals. The subject-matter of D4 belongs also to the medical field and document D4 can be therefore considered as the closest prior art for present application.

As stated above (point 2.2), the subject-matter of present claim 1 differs from the known composition in that it does not contain local anaesthetics.

The problem to be solved by the present invention may therefore be regarded as how to enhance mutually the topical absorption of at least two drugs, regardless their nature (see present application p. 1, l. 3-12 and p. 4, l. 8-18).

Document D4 teaches the skilled person that a composition comprising a eutectic mixture of local anaesthetics is chemically more stable: the active ingredients are less subject to hydrolytic degradation. Even though document D4 points out that the device can be used for delivering a multitude of drugs, the teaching of D4, regarding a eutectic mixture, is confined to anaesthetics and more particularly to the their stability (see D4, p. 10, l. 6 - p. 13, l. 7). There is no incentive in D4 to consider the applicability of a eutectic mixture for anything other than hydrolysis-sensitive local anaesthetics, and even less for increasing the mutual enhancement of the topical absorption of at least two drugs. In D4, the improvement of the dermal permeation is due to heat supplied by the device, regardless of the formulation, eutectic or non-eutectic. The present application does not require the use of heat to achieve a similar aim.

For these reasons, the subject-matter of independent claim 1 seems to include an inventive step in the meaning of Art. 33(3) PCT.

This reasoning applies mutatis mutandis to the subject-matter of present independent claim 22.

- 4 Claims 2-20 are dependent on independent claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.
- 5 For the assessment of the present claims 21 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IE98/00036

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (present claim 22).

VII

- 1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D3-D5 is not mentioned in the description, nor are these documents identified therein.
- 2 The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

O'CONNELL, Maura
F.R. KELLY & CO
9 University Street
Belfast BT7 1NA
Northern Ireland
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

14.03.99

Applicant's or agent's file reference
FB3782/MOC

IMPORTANT NOTIFICATION

International application No.
PCT/IE98/00036

International filing date (day/month/year)
14/05/1998

Priority date (day/month/year)
14/05/1997

Applicant

GALEN (CHEMICALS) LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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PATENT COOPERATION TREATY



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FB3782/MOC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IE98/00036	International filing date (day/month/year) 14/05/1998	Priority date (day/month/year) 14/05/1997
International Patent Classification (IPC) or national classification and IPC A61K9/107		
Applicant GALEN (CHEMICALS) LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 7 sheets.
3. This report contains indications relating to the following items: I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 14/12/1998	Date of completion of this report 14.03.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Simon, F Telephone No. +49 89 2399 2083 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IE98/00036

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20 as originally filed

Claims, No.:

1-24 as received on 20/08/1999 with letter of 19/08/1999

Drawings, sheets:

1-9 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 21.23.

because:

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- ☒ the said international application, or the said claims Nos. 21,23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-20,22
	No: Claims
Inventive step (IS)	Yes: Claims 1-20,22
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-20,22
	No: Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IE98/00036

I

The amendments filed with the letter dated 19.08.1999 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following: present claim 24 deals with eutectic mixtures of specific compounds. Even though said specific compounds are mentioned in examples A-I and examples 3 and 6 in the description as filed, said compounds are only disclosed in relation to a specific ratio for which the eutectic mixture is liquid at 20°C (see eg example B and fig. 2), in a specific composition (see example 3, "emulsified gel preparation suitable for treating allergic and inflammatory pruritic skin compositions") and only for exactly two compounds and not for at least two compounds. Present claim 24 does not refer to each of these features and its subject-matter is therefore broader than that disclosed in the application as filed.

III

The subject-matter of claims 21 and 23 is directed to a method for treatment of the human body by therapy (Art. 34(4)(a)(i) and Rule 67.1(iv) PCT).

V

1 Reference is made to the following documents:

D3: WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991

D4: WO 97 04728 A (ZHANG ET AL.) 13 February 1997

D5: A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US)

D6: EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992

2 Novelty (Art. 33(2) PCT)

The subject-matter of present claims 1-20 and 22 fulfills the requirements of Art. 33(2) PCT.

2.1 Document D3 (see D3, page 3, lines 3-10 and eg. example 3 on page 6)

discloses eg a composition containing a eutectic solution of 4 g ibuprofen and 4 g menthol, also mixed with benzyl alcohol, carbomer and water. However, none of the compositions of D3 contains an emulsifying agent. Therefore, the subject-matter of present independent claim 1 and present independent claim 22 is new over D3.

- 2.2 Document D4 discloses a formulation, which is a gelled oil-in-water emulsion with an oil phase being a eutectic mixture of local anaesthetics. In a particular embodiment (see D4, example 1, page 18), the composition comprises an aqueous continuous phase with a polymeric emulsifier and an oil phase consisting of a eutectic mixture of lipocaine and tetracaine stated as being liquid at room temperature. However, present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. Thus, present independent claims 1 and 22 are new over D4.
- 2.3 Document D5 discloses a topical anaesthetic formulation based on a 1:1 eutectic mixture, having an eutectic temperature of 18°C, of lidocaine and prilocaine, emulsified in water. Present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. For this reason, present independent claims 1 and 22 are new over D5.
- 2.4 Document D6 discloses a stabilized pesticidal emulsion of the oil-in-water type (see D6, page 4, lines 39-45) comprising (see D6, pages 20-21, example 3):
- an oil phase consisting of two pesticides: 191 g/l (2,4-dichlorophenoxy)acetic acid isooctyl ester (2,4-D IOE) and 208 g/l (2,4-dichlorophenoxy)propionic acid isooctyl ester (2,4-DP IOE),
 - a water phase containing surfactants and thickeners.
- Even though said pesticides are ingredients which are pharmacologically active and are liquid at room temperature (see D6, page 19, lines 33- 37 and page 7, lines 8-12), present independent claim 1 and present independent claim 22 refer to topical compositions for mutual enhancement of transdermal permeation of pharmacologically active ingredients. It is clear that compositions containing pesticides, ie substances which are virtually toxic to humans, are not topical compositions suitable for transdermal permeation in the meaning of the present application.

3 Inventive step (Art. 33(3) PCT)

Document D4 is devoted to an apparatus, a product formulation and a method for improved dermal permeation of pharmaceuticals. The subject-matter of D4 belongs also to the medical field and document D4 can be therefore considered as the closest prior art for present application.

As stated above (point 2.2), the subject-matter of present claim 1 differs from the known composition in that it does not contain local anaesthetics.

The problem to be solved by the present invention may therefore be regarded as how to enhance mutually the topical absorption of at least two drugs, regardless their nature (see present application p. 1, l. 3-12 and p. 4, l. 8-18).

Document D4 teaches the skilled person that a composition comprising a eutectic mixture of local anaesthetics is chemically more stable: the active ingredients are less subject to hydrolytic degradation. Even though document D4 points out that the device can be used for delivering a multitude of drugs, the teaching of D4, regarding a eutectic mixture, is confined to anaesthetics and more particularly to the their stability (see D4, p. 10, l. 6 - p. 13, l. 7). There is no incentive in D4 to consider the applicability of a eutectic mixture for anything other than hydrolysis-sensitive local anaesthetics, and even less for increasing the mutual enhancement of the topical absorption of at least two drugs. In D4, the improvement of the dermal permeation is due to heat supplied by the device, regardless of the formulation, eutectic or non-eutectic. The present application does not require the use of heat to achieve a similar aim.

For these reasons, the subject-matter of independent claim 1 seems to include an inventive step in the meaning of Art. 33(3) PCT.

This reasoning applies mutatis mutandis to the subject-matter of present independent claim 22.

- 4 Claims 2-20 are dependent on independent claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.
- 5 For the assessment of the present claims 21 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

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International application No. PCT/IE98/00036

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (present claim 22).

VII

- 1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D3-D5 is not mentioned in the description, nor are these documents identified therein.
- 2 The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

CLAIMS

1. A topical composition for mutual enhancement of transdermal permeation of at least first and second pharmacologically active agents, the composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics.

2. A topical composition according to Claim 1, in which the first pharmacologically active agent has a melting point between 35 and 75°C, preferably 40-50°C, and the second pharmacologically active agent has a melting point between -40°C and 150°C, preferably between -5 and 90°C.

3. A topical composition according to Claim 1 or 2, in which the topical composition additionally includes, in the eutectic mixture, a third pharmaceutically acceptable component.

4. A topical composition according to Claim 3, in which the third pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.

5

5. A topical composition according to Claim 3 or 4, in which the third component is a third pharmacologically active agent.

10 6. A topical composition according to any one of Claims 3-5, in which the topical composition additionally includes, in the eutectic mixture, a fourth pharmaceutically acceptable component.

15 7. A topical composition according to Claim 6, in which the fourth pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.

20 8. A topical composition according to Claim 6 or 7, in which the fourth component comprises a fourth pharmacologically active agent.

9. A topical composition according to any one of
25 the preceding claims, in which said at least one discontinuous phase contains no co-solvent or additional oil phase, so that the eutectic mixture substantially, preferably essentially, comprises the or each discontinuous phase of the emulsion.

10. A topical composition according to any one of the preceding claims, in which the first pharmacologically active agent is selected from
5 triclosan, chlorocresol, chlorbutanol, methyl nicotinate, triprolidine, promethazine, trimeprazine, sulfiram, oxybutynin, capsaicin, testosterone enanthate or choline salicylate.

10 11. A topical composition according to any one of the preceding claims, in which the second pharmacologically active agent is selected from triclosan; chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate; non-steroid anti-inflammatory agents
15 selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and
20 ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; anthelmintics such as tetramisole; antihistaminics such as triprolidine and promethazine and antihypertensives such as propranolol.

25

12. A topical composition according to Claim 5 or 8, in which the third and fourth pharmacologically active agents are each selected from triclosan; chlorocresol; capsaicin, trimeprazine, choline salicylate, methyl

nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and
5 arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; antihypertensives such as
10 propranolol; antihistaminics such as triprolidine and promethazine; and anthelmintics such as tetramisole.

13. A topical composition according to Claim 3 or 4, in which the third component is a pharmaceutically
15 acceptable component selected from lauric acid, stearyl alcohol, menthol, thymol, cinnamic acid or an ester thereof.

14. A topical composition according to any one of the
20 preceding claims, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier containing substantially, preferably essentially, water as the continuous phase.

25 15. A topical composition according to any one of the preceding claims, in which the pharmaceutically acceptable carrier contains at least one gelling or suspension agent.

16. A topical composition according to Claim 15, in which the gelling or suspension agent is selected from carbomers, modified cellulose derivatives, naturally-
5 occurring, synthetic or semi-synthetic gums such as xanthan gum, acacia and tragacanth, modified starches, co-polymers such as those formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylate derivatives or a mixture thereof.

10

17. A topical composition according to any one of the preceding claims, in which the topical composition is in the form of a gel, lotion, suspension, cream, aerosol spray, transdermal patch, medicated dressing or
15 soft gelatin capsule.

18. A topical composition according to any one of the preceding claims, in which the emulsifying agent is selected from non-ionic, cationic and anionic
20 surfactants.

19. A topical composition according to Claim 18, in which the emulsifying agent is a non-ionic surfactant.

25 20. A topical composition according to any one of the preceding claims, in which the at least two pharmacologically active agents are structurally and/or pharmacologically diverse.

21. Use of a topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of at least first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics, for mutual enhancement of transdermal permeation of the at least first and second pharmacologically active agents.

22. Use of an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of at least first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics, for the manufacture of a topical composition for mutual enhancement of dermal permeation of the at least first and second pharmacologically active agents.

AMENDED SHEET

23. A method for mutual enhancement of dermal permeation of at least first and second pharmacologically active agents, the method comprising applying a topical composition for mutual enhancement of transdermal permeation of at least first and second pharmacologically active agents, the composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics, to an accessible body surface.

24. A topical composition according to any one of the preceding claims in which the eutectic mixture of at least two pharmacologically active agents is selected from the group consisting of ibuprofen - methyl nicotinate, oxybutynin - chlorbutol, triclosan - oxybutynin, methyl cinnamate - oxybutynin, chlorobutol - testosterone enanthate, methyl nicotinate - ketoprofen, triclosan - econazole, sulfiram - levamisole, promethazine - triclosan, promethazine - benzocaine and ketoprofen - benzocaine.

AMENDED SHEET

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IE 98/00036

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K9/107 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991 see page 5; example 1 ---	1, 2, 9, 14-18 3-8, 10-13
X	WO 97 04728 A (ZHANG ET AL.) 13 February 1997 see page 18, line 14 - line 31 ---	1, 2, 9, 14-18
X	A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US) see page 365 --- -/-	1, 2, 9, 14-18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

*** Special categories of cited documents:**

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

28 September 1998

Date of mailing of the international search report

08/10/1998

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IE 98/00036

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992 see page 7, line 8 - line 12 see page 20 - page 21; example 3 -----</p>	1, 2, 9, 14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IE 98/00036

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9104733 A	18-04-1991	AU 6504190 A	28-04-1991
		CA 2067131 A	27-03-1991
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